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Description

Background of the invention

1. Field of the invention

This invention relates to novel three-layered pharmaceutical film preparations and processes for the production thereof. More specifically, this invention relates to the three-layered pharmaceutical film preparations which comprise one drug-storing middle layer composed of water soluble polymers and therapeutically active ingredients (prostaglandin analogues), and a release-controlling layer on each side of the said middle layer, composed of water soluble polymers, characterized by that the prostaglandin analogues contained therein exhibit the desired long-lasting release pattern, further fully satisfying the purpose that drug preparations which have very high biological availability and are effective and safe should be supplied, as well as the novel processes for production thereof.

2. Description of the prior art

Various techniques for releasing drug for an extended period of time have heretofore been reported in the literature. For instance, there are known coating methods to maintain release for an extended period of time, as found mainly in oral tablets, intravaginal devices, drug release devices utilizing the osmotic pressure and dispensers utilizing semipermeable membranes or porous membranes. In more recent years, there have also been reported the development of polymers for achieving long-lasting release intended for topical applications, long-lasting films and containers for releasing the drug quantitatively by release from one side; in any case, however, they have disadvantages that high levels of techniques and equipment are required and that the form of that device (preparation) is retained even in the body (administration site) so that the patient can feel it. Further, they also have such disadvantages that the expected drug efficacy is difficult to obtain because the stability of the active ingredient is adversely affected and the biological availability is low. To eliminate these disadvantages, there are film preparations and preparations like cellulose fiber to obtain long-lasting release by using cellulose ether soluble in body fluid (see Japanese Patent Kokai No. 49-133519, Derwent No. 47633V). Although the form of the said preparations is not retained in the administration site, they have disadvantages that high levels of techniques and equipment, and further high temperature in the production process are required, and, therefore, it is considered that the stability of the active ingredient is adversely affected by high temperature in case of the production of the preparation containing prostaglandin analogues.

In more recent years, we have proposed multi-layered pharmaceutical film preparations which comprise water soluble polymer bases and water insoluble polymer bases, for the purpose of maintaining the release of a drug for an extended period of time (see Japanese Patent Kokai No. 57-70816, Derwent No. 35619E). However, though these pharmaceutical film preparations are improved, they still have disadvantages that the biological availability is not sufficient, the lasting time of release is short, and the release tends to be "sigmoid release" (S-shaped release). Therefore, it can not be said that they are satisfactory film preparations.

On the other hand, there are known several methods for the production of a film using hydroxypropyl cellulose (abbreviated HPC hereafter). That is to say, as processes for the production of the films using HPC, there are known a process dissolving HPC in a suitable organic solvent and then evaporating the solvent, and a process dissolving HPC in water and then evaporating water (see Japanese Patent Kokoku No. 56-36173, Derwent No. 43052W). The said processes are very useful when the HPC used has a relatively small molecular weight, e.g. 30,000—150,000 and low viscosity. However, there is a possibility of various problems when the HPC used has the molecular weight of 250,000—400,000 and high viscosity.

For example, practically speaking, the upper limit of the solubility of HPC having the molecular weight of 250,000—400,000 (abbreviated HPC-H hereafter) in water or methanol is 4% and, therefore, a HPC-H solution having a thickness of 1 mm becomes an HPC-H film having a thickness of only about 0.04 mm after evaporation. Accordingly, it is necessary to use an HPC-H solution having a thickness of about 7.5 mm in order to obtain a HPC-H film having a thickness of 0.3 mm which is the preferred thickness for the release-controlling layers in the pharmaceutical film preparation of the present invention. However, the increase in the volume of solvent used causes various problems, so that a film having uniform thickness can not be obtained, it takes a lot of time to dry the film, the film is difficult to dry completely, and further, that the environment in or out of the laboratory is polluted. Particularly, the difficulty in removing bubbles owing to the high viscosity becomes a large obstacle to the mass production.

Summary of the invention

Accordingly, an object of the present invention is to provide new three-layered pharmaceutical film preparations which have eliminated the disadvantages of the conventional techniques, that is, which may release the drug at the desired concentration lastingly for an extended period of time, with great high biological availability, and can make this release "zero-order release" (straight-line release), and further have improved the stability of the prostaglandin analogues contained therein, and in which the form of the preparation is not retained at the administered site (in the vagina) after administration.

Furthermore, another main object of the present invention is to provide processes for the production of the pharmaceutical film prepara-

tions of the present invention, in particular new processes for the production of release-controlling layers in the said film preparations using HPC-H. That is to say, the present invention also provides new processes for the production of the HPC-H film having a suitable thickness by using a small amount of solvent.

Brief description of the drawing

The drawing is a graph showing the percent dissolution of the prostaglandin analogues in various preparations.

Detailed description of the invention

The present invention provides three-layered pharmaceutical film preparations which comprise one drug-storing middle layer containing therapeutically active ingredients, and a release-controlling layer on each side of the said middle layer, controlling the release of the prostaglandin analogue. The size is preferably such that the surface area (the sum of the surface areas of the release-controlling layers on the both sides) is 2—20 cm^2 and the thickness is 0.3—3.0 mm, especially size of 5—15 cm^2 in surface area and 0.6—1.5 mm in thickness being desired.

The drug-storing middle layers in the pharmaceutical film preparations of the present invention, are composed of one or more (a) polyvinylpyrrolidones (abbreviated PVP hereafter), (b) HPCs, (c) plasticizers and (d) organic acids and contain required amounts of the prostaglandin analogue.

Various standardized PVP are commercially available, according to its molecular weights. For example, Kollidon-17 (molecular weight; ca. 11,500), Kollidon-30 (molecular weight; ca. 40,000) and Kollidon-90 (molecular weight; ca. 360,000) (registered Trade Marks and prepared by BASF A.G.) etc. are on the market. Any standardized PVP mentioned above or a combination of two or more of them may be used in the drug-storing middle layer, and PVP having the molecular weight of 300,000—400,000 is preferred. Kollidon-90 is most preferred.

Various standardized HPCs also commercially available, according to molecular weight. For example, besides HPC-H hereinbefore mentioned, HPC-M (molecular weight; 110,000—150,000), HPC-L (molecular weight; 55,000—70,000) and HPC-SL (molecular weight; 30,000—50,000) (registered Trade Marks and prepared by Nippon Soda K.K.) are on the market. Any standardized HPC mentioned above or a combination of two or more of them may be used as the drug-storing middle layer, and HPC-H is preferred. The amount of HPC to be added is preferably such that it is added to the drug-storing middle layer in a proportion of 5—30% by weight, more preferably 5—10%.

The plasticizers used in the drug-storing middle layer, include biologically inactive, conventional plasticizers, for example, propylene glycol, glycerol, polyethylene glycol and lauryl alcohol, or a combination of two or more of them, preferably polyethylene glycol or lauryl alcohol. Since plasticizers make the films more flexible, physical difficulty in the administration site may be prevented. The amount of the plasticizer is preferably such that it is added to the drug-storing middle layer in a proportion of 10—40% by weight, more preferably 25—35% by weight.

The prostaglandin analogues in the drug-storing middle layer include prostaglandin F compounds and prostaglandin E compounds having uterine contractile activity, and preferably are prostaglandin F and prostaglandin E analogues showing induction of menstruation, abortion or induction of labour by intravaginal administration, and more preferably 16,16 - dimethyl - *trans* - Δ^2 - PGE_1 methyl ester (abbreviated ONO-802 hereafter).

The organic acid used in the drug-storing middle layer may contribute to the stability of the prostaglandin analogues, and citric acid and tartaric acid are effective, and therefore preferred. The amount of the organic acid is preferably such that it is added to the drug-storing middle layer in a proportion of 0.05—0.3% by weight.

Generally, PVP has poor plasticity, and is solid and brittle, but the addition of HPC and plasticizers in a suitable proportion gives it proper flexibility, and eases plasticity. In order to improve plasticity, for example, the addition of a suitable amount of HPC-H and polyethylene glycol or lauryl alcohol as a plasticizer to Kollidon-90 is preferred. The total amount of HPC and the plasticizer to be added may be less than 50% by weight in the drug-storing middle layer.

The drug-storing middle layer may be obtained by dissolving one or more PVPs, HPCs and plasticizers in an organic solvent such as a lower alkanol, e.g. methanol or ethanol, or mixture of a lower alkanol and acetone, and, when a transparent solution is formed, adding a prostaglandin solution containing an organic acid dissolved in such an organic solvent as above mentioned, and after a homogeneous solution is formed, deaerating it sufficiently, and further drying by a conventional method to remove the organic solvent.

On the other hand, the release-controlling layers in the three-layered pharmaceutical film preparations of the present invention, are composed of one or more (a) HPCs and (b) plasticizers. While the release-controlling layers most often do not contain any active ingredients, it is possible to incorporate a minor amount of the prostaglandin analogue in them where it is necessary to release the prostaglandin analogue at an earlier stage after administration.

The HPC used in the release-controlling layers includes various standardized HPCs mentioned above, alone or a combination of two or more of them, and HPC-H is most preferred in order to obtain moderate release rate and long term release.

The plasticizers used in the release-controlling layers include various plasticizers mentioned above, alone or the combination of two or more

of them, preferably propylene glycol or glycerol. The amount of the plasticizer is preferably such that it is added to the release-controlling layer at a proportion of 5—15% by weight.

When various standardized HPC other than HPC-H is used as a base of the release-controlling layer, the release-controlling layer may be obtained by dissolving one or more HPCs and plasticizers in a proper organic solvent such as a lower alkanol, e.g. methanol or ethanol, or a mixture of a lower alkanol and acetone, and, if desired, adding a prostaglandin solution containing an organic acid dissolved in such an organic solvent as above mentioned and, when a homogeneous solution is formed, deaerating it sufficiently, and further drying by a conventional method to remove the organic solvent.

It is previously pointed out that, if the release-controlling layer composed of HPC-H is produced by the same procedure as mentioned for that composed of HPC other than HPC-H, various problems should occur. The present invention, furthermore, provides a new process for the production of the release-controlling layer composed of HPC-H having a suitable thickness by using a small amount of solvent. We have found that the release-controlling layer composed of HPC-H may be obtained most advantageously by utilizing the property that HPC-H can dissolve in water at a temperature below 40°C, but does not dissolve in it at a temperature more than 45°C. That is to say, the release-controlling layer composed of HPC-H may be obtained by adding one or more plasticizers, and HPC-H in hot water, preferably water warmed at 75—80°C, suspending the mixture so as to homogeneously disperse, and if desired, adding a prostaglandin solution containing an organic acid dissolved in a small amount of an organic solvent such as a lower alkanol, e.g. methanol or ethanol, or a mixture of a lower alkanol and acetone, and spreading out the obtained suspension as a layer having a uniform thickness, and lowering its temperature below 45°C to obtain a homogeneous solution layer owing to the swell of HPC-H, and raising its temperature to 60—70°C again to dry and remove water. By this method, the release-controlling layers which have no bubbles therein, and have flexibility and the desired thickness, may be easily obtained.

The three-layered pharmaceutical film preparations of the present invention may be obtained by mounting two release-controlling layers and one drug-storing middle layer obtained by the above methods, putting the drug-storing middle layer between two release-controlling layers, by a dry laminating method, e.g. by heating, or by a wet laminating method, e.g. by using a suitable organic solvent such as methanol or ethanol, or using a solution of HPC in a suitable organic solvent such as methanol or ethanol.

The three-layered pharmaceutical film preparations of the present invention are suitable for the administration to the mucosal tissue in the body cavity, particularly for intravaginal administration.

When the three-layered pharmaceutical film preparations of the present invention are administered to the mucosal tissue in the body cavity, they are swollen with the body liquid and expanded about ten times. Then the body liquid permeates into the drug-storing middle layer without decomposing the release-controlling layers and dissolves gradually the drug-storing middle layer, and the drug containing therein is leached out to show "zero-order release". Thereafter the release-controlling layers are dissolved gradually by the body liquid. Therefore, an ideal release pattern lasting for an extended period of time and high biological availability may be obtained.

In the three-layered pharmaceutical film preparations of the present invention, the release rate of the drug and the lasting time of the release suitable for the expected drug efficacy may be optionally established, (i) by changing the kind of HPC constituting the release-controlling layers or changing the constitutional ratio of HPC in the case where two or more HPCs are used, (ii) by changing the surface area and/or thickness of the release-controlling layers, (iii) by changing the kind of PVP and/or HPC constituting the drug-storing middle layer, or changing the constitutional ratio of them in the case where two or more of PVPs or HPCs are used, (iv) by changing the surface area and/or thickness of the drug-storing middle layer, (v) by changing the amount of the drug included in the drug-storing middle layer, and/or (vi) by incorporating the drug in the release-controlling layers.

The features of the three-layered pharmaceutical film preparations obtained according to the present invention are as follows:

(1) Since the drug is released passing through the release-controlling layer having little change of the surface area after swelling, the release is nearly a form of zero-order release and is an almost ideal release pattern.

(2) Since the biological availability is very high and hence a dosage level of the drug may be low, high effectiveness may be exhibited without the possibility of overdose.

(3) Since a constant release pattern of the drug is obtained regardless of the individuals, safer preparations may be obtained.

(4) Since the film preparations of the present invention apply to the administration to the body cavity and hence they are gradually dissolved by the body liquid after releasing the desired drug, the shape of the preparations does not remain and, therefore, there is unnecessary to remove it after use.

(5) During the film formation step, by addition of PVP, HPC, plasticizers and organic acids, unstable prostaglandin analogues are hardly decomposed and, therefore, the stability can be retained for an extended period of time.

(6) The release-controlling layers which have no bubbles therein, and have the uniform and

desired thickness, may be easily prepared by suspending and dispersing HPC-H having high viscosity and high molecular weight in hot water at 75—80°C, and then lowering its temperature below 45°C.

The size, shape and thickness of the three-layered pharmaceutical film preparation of the present invention may be properly established depending on the pharmacological properties of the prostaglandin analogues contained therein, the purpose for use, and may be prepared using a conventional process for producing multi-layered film preparations.

The present invention is more fully described by the following examples and experimental example.

Example 1

(a) Preparation of a release-controlling layer

15 g of propylene glycol were added to 240 ml of distilled water. The solution was fully warmed on water bath at 80°C, and thereto were added with storing little by little 135 g of HPC-H previously sieved through a 200-mesh sieve, and then the mixture was stirred for about 15 minutes to obtain a suspension homogeneously dispersed. The suspension was quickly poured into and spread out in a tray which was previously warmed at 80°C. After lowering its temperature below 45°C, the homogeneous layer is changed into a homogeneous liquid layer by its swelling. The obtained liquid layer were fully dried in an oven at 60°—70°C. The film thus prepared was cut out to obtain about 1,000 sheets of the film being about 6.2 cm^2 in area and about 0.2 mm in thickness.

(b) Preparation of a drug-storing layer

118.3 g of Kollidon-90, 20 g of HPC-H, 20 g of polyethylene glycol 2000 (registered Trade Mark, prepared by Nippon Oils and Fats Co., Ltd.) and 40 g of polyethylene glycol 600 (registered Trade Mark, prepared by Nippon Oils and Fats Co., Ltd.) were, successively, dissolved in 1.9 liters of methanol with stirring at room temperature to obtain a homogeneous solution. To the solution, was added a solution of 1.5 g of ONO-802 and 0.2 g of citric acid in 100 ml of methanol and, thereafter, the solution was stirred fully and allowed to stand for effecting deaeration. The solution thus obtained was poured into a tray which was previously warmed at 40°C, with paying attention for bubbles not to enter thereto, and dried in an oven. The film thus prepared was cut out to obtain about 1,000 sheets of the film being about 6.2 cm^2 in area and about 0.2 mm in thickness.

(c) Production of a three-layered film preparation

Two sheets of the film of the release-controlling layer obtained in the above (a) were laminated by heating with one sheet of the film of the drug-storing layer obtained in the above (b), placed therebetween to obtain a three-layered film preparation being about 0.7 mm in thickness.

Example 2

(a) Preparation of a release-controlling layer

About 1,000 sheets of the film of the release-controlling layer, being about 0.3 mm in thickness and about 6.2 cm^2 in area were obtained similarly as Example 1 (a) by using 22.5 g of glycerol instead of propylene glycol employed in Example 1 (a), and 360 ml of distilled water and 202.5 g of HPC-H.

(b) Preparation of a drug-storing middle layer

About 1,000 sheets of the film of the drug-storing middle layer, being about 0.3 mm in thickness and about 6.2 cm^2 in area were obtained similarly as Example 1 (b) by using 60 g of lauryl alcohol instead of polyethylene glycol 2000 and polyethylene glycol 600 which were employed in Example 1 (b), using 0.6 g of tartaric acid instead of citric acid which was employed in Example 1 (b), and further using 2 liters of methanol, 117.9 g of Kollidon-90, 20 g of HPC-H and 1.5 g of ONO-802.

(c) Production of a three-layered film preparation

Two sheets of the film of the release-controlling layer obtained in the above (a) were laminated with a 2.5% solution of HPC in methanol, with one sheet of the film of the drug-storing middle layer obtained in the above (b), placed therebetween to obtain a three-layered film preparation being about 0.9 mm in thickness.

Example 3

(a) Preparation of a release-controlling layer

About 1,000 sheets of the film of the release-controlling layer, being about 0.35 mm in thickness and about 6.2 cm^2 in area were obtained similarly as Example 1 (a) by using 416 ml of distilled water, 26 g of propylene glycol and 234 g of HPC-H.

(b) Production of a three-layered film preparation

Two sheets of the film of the release-controlling layer contained in the above (a) were laminated with a 2.5% solution of HPC in methanol, with one sheet of the film of the drug-storing layer obtained in Example 1 (b), placed therebetween to obtain a three-layered film preparation being about 0.9 mm in thickness.

Experimental Example

In order to compare the following preparations: the three-layered film preparation of the present invention, prepared in Example 1 and Example 3 (abbreviated L-HP film-(1) and L-HP film-(3), respectively, hereafter); a single-layered film preparation employing a water soluble polymer (prepared similarly as the description of Example 1 of the specification of Japanese Patent Kokai No. 56-34619, Derwent No. 37166D, using 199.5 mg of HPC-L, 0.2 mg of ONO-802 and 0.3 mg of citric acid; abbreviated HPC film hereafter); and a multi-layered film preparation employing a water soluble polymer and a water insoluble polymer (prepared similarly as the description of example

1 of the specification of Japanese Patent Kokai No. 57-70816, Derwent No. 35619E, using 1.2 g of vinyl acetate resin, 2.4 g of HPC, 0.2 g of glycerol and 0.2 of triacetin for preparing drug release-controlling layers, and using 1.88 g of HPC, 10 mg of glycerol, 0.1 g of triacetin, 10 mg of ONO-802 and 3 mg of tartaric acid for preparing a drug-storing middle layer; abbreviated N-HP film hereafter), for the release rate of the drug and the long-lasting properties of the release, a dissolution test was conducted according to the modified USP paddle method (details of experiments are described hereafter). The results of the experiments are shown in Table 1 and Fig. 1.

Modified USP paddle method

700 ml of distilled water was placed in a flask and warmed at 37±0.5°C. 5-mesh wire was settled at the bottom of the flask, and thereon a sheet of tested film preparationn putting between two sheets of 60-mesh wire net was placed, and thereafter the solution in the flask was stirred at 25 r.p.m. At regular time intervals, 30 ml of the dissolution solution was withdrawn and 30 ml of distilled water previously warmed at 37±0.5°C was added in the flask. To the dissolution solution withdrawn was added exactly 2 ml of internal standard solution (i.e. a 0.001% corticosterone acetate solution in acetonitrile). The solution was extracted with 10 ml of ethyl acetate twice (total: 20 ml) and the extract was concentrated under reduced pressure. To the residue was added 0.1 ml of a 80% acetonitrile solution to use as HPLC (High Performance Liquid Chromatography) sample solution.

TABLE 1

Percent dissolution (%) in various preparations

Sample	Dissolution time (hr)									
	1/2	3/4	1	2	3	4	6	8	10	12
HPC film (Comparison)	43	83								
N-HP film (Comparison)				28	58	69	74			
L-HP film-(1) (Invention)			4	12		30	46	61	78	90
L-HP film-(3) (Invention)					15	21		45		

Claims for the Designated States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A three-layered pharmaceutical film preparation which comprises one drug-storing middle layer composed of one or more (a) polyvinylpyrrolidone, (b) hydroxypropyl celluloses, (c) plasticizers and (d) organic acids, containing prostaglandin analogue, and a release-controlling layer on each side of the said middle layer, composed of one or more (a) hydroxypropyl celluloses and (b) plasticizers, containing or not containing prostaglandin analogue.

2. A three-layered pharmaceutical film preparation according to claim 1, wherein the release-controlling layer does not contain prostaglandin analogues.

3. A three-layered pharmaceutical film preparation according to claim 1, wherein the release-controlling layer contains prostaglandin analogues.

4. A three-layered pharmaceutical film preparation according to claim 2 or 3, wherein the molecular weight of polyvinylpyrrolidone is 300,000—400,000.

5. A three-layered pharmaceutical film preparation according to claim 2 or 3, wherein the molecular weight of hydroxypropyl cellulose is 250,000—400,000.

6. A three-layered pharmaceutical film preparation according to claim 2 or 3, wherein the plasticizer is propylene glycol, glycerol, polyethylene glycol or lauryl alcohol.

7. A three-layered pharmaceutical film preparation according to claim 2 or 3, wherein the organic acid is citric acid or tartaric acid.

8. A three-layered pharmaceutical film preparation according to claim 2 or 3, wherein the prostaglandin analogue is a prostaglandin F compound or a prostaglandin E compound.

9. A three-layered pharmaceutical film preparation according to claim 2, wherein the drug-storing middle layer is composed of (a) polyvinylpyrrolidone having the molecular weight of 300,000—400,000, (b) hydroxypropyl cellulose having the molecular weight of 250,000—400,000, (c) polyethylene glycol and (d) citric acid, containing 16,16 - dimethyl - *trans* - Δ^2 - PGE_1 methyl ester, and the release-controlling layer is composed of (a) hydroxypropyl cellulose having the molecular weight of 250,000—400,000 and (b) propylene glycol.

10. A three-layered pharmaceutical film preparation according to claim 2, wherein the drug-storing middle layer is composed of (a) polyvinylpyrrolidone having the molecular weight of 300,000—400,000, (b) hydroxypropyl cellulose having the molecular weight of 250,000—400,000, (c) lauryl alcohol and (d) tartaric acid, containing 16,16 - dimethyl -

trans - Δ^2 - PGE_1 methyl ester, and the release-controlling layer is composed of (a) hydroxypropyl cellulose having the molecular weight of 250,000—400,000 and (b) glycerol.

11. A process for producing three-layered pharmaceutical film preparations which is characterized by mounting, by a laminating method, two sheets of a film of a release-controlling layer obtained by dissolving one or more hydroxypropyl celluloses having a molecular weight of 30,000—150,000 and one or more plasticizers in an organic solvent, and optionally adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method, and one sheet of a film of a drug-storing layer obtained by dissolving one or more polyvinylpyrrolidone, hydroxypropyl cellulose and plasticizers in an organic solvent, and adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method.

12. A process for producing three-layered pharmaceutical film preparations which is characterized by mounting, by a laminating method, two sheets of a film of a release-controlling layer obtained by adding one or more plasticizers and hydroxypropyl celluloses having a molecular weight of 250,000—400,000 in hot water, and suspending and dispersing homogeneously, and optionally adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and spreading out the obtained suspension as a layer having the uniform thickness, and then lowering its temperature below 45°C to obtain a homogeneous solution layer, and thereafter drying it with heating, and one sheet of a film of a drug-storing layer obtained by dissolving one or more polyvinylpyrrolidones, hydroxypropyl celluloses and plasticizers in an organic solvent, and adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method.

Claims for the Designated State: AT

1. A device for administering a prostaglandin analogue, which is a three-layered structure comprising one drug-storing middle layer composed of one or more (a) polyvinylpyrrolidones, (b) hydroxypropyl celluloses, (c) plasticizers and (d) organic acids, containing prostaglandin analogue, and a release-controlling layer on each side of the said middle layer, composed of one or more (a) hydroxypropyl celluloses and (b) plasticizers, containing or not containing prostaglandin analogue.

2. A device according to claim 1, wherein the release-controlling layer does not contain prostaglandin analogues.

3. A device according to claim 1, wherein the release-controlling layer contains prostaglandin analogues.

4. A device according to claim 2 or 3, wherein the molecular weight of polyvinylpyrrolidone is 300,000—400,000.

5. A device according to claim 2 or 3, wherein the molecular weight of hydroxypropyl cellulose is 250,000—400,000.

6. A device according to claim 2 or 3, wherein the plasticizer is propylene glycol, glycerol, polyethylene glycol or lauryl alcohol.

7. A device according to claim 2 or 3, wherein the organic acid is citric acid or tartaric acid.

8. A device according to claim 2 or 3, wherein the prostaglandin analogue is a prostaglandin F compound or a prostaglandin E compound.

9. A device according to claim 2, wherein the drug-storing middle layer is composed of (a) polyvinylpyrrolidone having the molecular weight of 300,000—400,000, (b) hydroxypropyl cellulose having the molecular weight of 250,000—400,000, (c) polyethylene glycol and (d) citric acid, containing 16,16 - dimethyl - *trans* - Δ^2 - PGE_1 methyl ester, and the release-controlling layer is composed of (a) hydroxypropyl cellulose having the molecular weight of 250,000—400,000 and (b) propylene glycol.

10. A device according to claim 2, wherein the drug-storing middle layer is composed of (a) polyvinylpyrrolidone having the molecular weight of 300,000—400,000, (b) hydroxypropyl cellulose having the molecular weight of 250,000—400,000, (c) lauryl alcohol and (d) tartaric acid, containing 16,16 - dimethyl - *trans* - Δ^2 - PGE_1 methyl ester, and the release-controlling layer is composed of (a) hydroxypropyl cellulose having the molecular weight of 250,000—400,000 and (b) glycerol.

11. A process for producing three-layered pharmaceutical film preparations which is characterized by mounting, by a laminating method, two sheets of a film of a release-controlling layer obtained by dissolving one or more hydroxypropyl celluloses having a molecular weight of 30,000—150,000 and one or more plasticizers in an organic solvent, and optionally adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method, and one sheet of a film of a drug-storing layer obtained by dissolving one or more polyvinylpyrrolidone, hydroxypropyl cellulose and plasticizers in an organic solvent, and adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method.

12. A process for producing three-layered pharmaceutical film preparations which is characterized by mounting, by a laminating method, two sheets of a film of a release-controlling layer obtained by adding one or more plasticizers and hydroxylpropyl celluloses having molecular weight of 250,000—400,000 in hot water, and suspending and dispersing homogeneously, and optionally adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and spreading out the obtained suspension as a layer having the uniform

thickness, and then lowering its temperature below 45°C to obtain a homogeneous solution layer, and thereafter drying it with heating, and one sheet of a film of a drug-storing layer obtained by dissolving one or more polyvinylpyrrolidones, hydroxypropyl celluloses and plasticizers in an organic solvent, and adding a prostaglandin solution containing an organic acid dissolved in an organic solvent, and deaerating it, and further drying by a conventional method.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutisches Dreilagen-Filmpräparat mit einer heilmittelspeichernden mittleren Lage bestehend aus einem oder mehreren (a) Polyvinylpyrrolidonen, (b) Hydroxypropylzellulosen, (c) Plastifizierungsmitteln und (d) organischen Säuren, enthaltend ein Prostaglandinanalog, und mit einer freisetzungssteuernden Lage auf jeder Seite der genannten mittleren Lage bestehend aus einem oder mehreren (a) Hydroxypropylzellulosen und (b) Plastifizierungsmitteln, ein Prostaglandinanalog enthaltend oder nicht.

2. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 1, dadurch gekennzeichnet, daß die freisetzungssteuernde Lage keine Prostaglandinanaloge enthält.

3. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 1, dadurch gekennzeichnet, daß die freisetzungssteuernde Lage Prostaglandinanaloge enthält.

4. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Polyvinylpyrrolidon ein Molekulargewicht zwischen 300 000 und 400 000 hat.

5. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die Hydroxypropylzellulose ein Molekulargewicht zwischen 250 000 und 400 000 hat.

6. Pharmazeutisches Dreiligen-Filmpräparat nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Plastifizierungsmittel Propylenglykol, Glycerin, Polyethylenglykol oder Laurylalkohol ist.

7. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die organische Säure Zitronensäure oder Weinsäure ist.

8. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Prostaglandinanalog eine Prostaglandin F-Verbindung oder eine Prostaglandin E-Verbindung ist.

9. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2, dadurch gekennzeichnet, daß die heilmittelspeichernde mittlere Lage aus (a) Polyvinylpyrrolidon mit einem Molekulargewicht von 300 000—400 000, (b) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000, (c) Polyethylenglykol und (d) Zitronensäure besteht, enthaltend 16,16 - Dimethyl - *trans* - Δ^2 - PGE^1 - methylester, und die freisetzungssteuernde Lage aus (a) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000 und (b) Propylenglykol besteht.

10. Pharmazeutisches Dreilagen-Filmpräparat nach Anspruch 2, dadurch gekennzeichnet, daß die heilmittelspeichernde mittlere Lage aus (a) Polyvinylpyrrolidon mit einem Molekulargewicht von 300 000—400 000, (b) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000, (c) Laurylalkohol und (d) Weinsäure besteht, enthaltend 16,16 - Dimethyl - *trans* - Δ^2 - PGE_1 - methylester, und die freisetzungssteuernde Lage aus (a) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000 und (b) Glycerin besteht.

11. Verfahren zur Herstellung eines pharmazeutischen Dreilagen-Filmpräparates, dadurch gekennzeichnet, daß mit Hilfe eines Schichtstoff-Herstellungsverfahrens zusammengebaut werden: zwei filmartige Blätter einer freisetzungssteuernden Lage, die man erhält, indem eine oder mehrere Hydroxypropylzellulosen mit einem Molekulargewicht von 30 000—150 000 und ein oder mehrere Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, gewünschtenfalls eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigemischt wird, und diese entlüftet und weiters mit Hilfe eines herkömmlichen Verfahrens getrocknet wird, und ein Blatt eines Films einer heilmittelspeichernden Lage, die man erhält, indem ein oder mehrere Polyvinylpyrrolidone, Hydroxypropylzellulosen und Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigemischt wird, diese entlüftet und weiters mit Hilfe eines herkömmlichen Verfahrens getrocknet wird.

12. Verfahren zur Herstellung eines pharmazeutischen Dreilagen-Filmpräparates, dadurch gekennzeichnet, daß mit Hilfe eines Schichtstoff-Herstellungsverfahrens zusammengebaut werden: zwei filmartige Blätter einer freisetzungssteuernden Lage, die man erhält, indem ein oder mehrere Plastifizierungsmittel und Hydroxyzellulosen mit einem Molekulargewicht von 250 000—400 000 in heißem Wasser beigemischt und homogen, suspendiert und dispergiert werden, gewünschtenfalls eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, zugesetzt wird, die erhaltene Suspension als eine Schicht mit einheitlicher Dicke ungebreitet und dann ihre Temperatut auf unter 45°C gesenkt wird, um eine homogene Lösungsschicht zu erhalten, und diese dann durch Erwärmen getrocknet wird, und ein filmartiges Blatt einer heilmittelspeichernden Lage, die man erhält, indem ein oder mehrere Polyvinylpyrrolidone, Hydroxypropylzellulosen und Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigmeischt wird, und diese entlüftet und weiters mit

Hilfe eines herkömmlichen Verfahrens getrocknet wird.

Patentansprüche für den Vertragsstaat: AT

1. Vorrichtung zur Verabreichung eines Prostaglandinanalogs, das eine dreilagige Struktur ist, mit einer heilmittelspeichernden mittleren Lage bestehend aus einem oder mehreren (a) Polyvinylpyrrolidonen, (b) Hydroxypropylzellulosen, (c) Plastifizierungsmitteln und (d) organischen Säuren, enthaltend ein Prostaglandinanalog, und mit einer freisetzungssteuernden Lage auf jeder Seite der genannten mittleren Lage bestehend aus einem oder mehreren (a) Hydroxypropylzellulosen und (b) Plastifizierungsmitteln, ein Prostaglandinanalog enthaltend oder nicht.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß die freisetzungssteuernde Lage keine Prostaglandinanaloge enthält.

3. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß die freisetzungssteuernde Lage Prostaglandinanaloge enthält.

4. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Polyvinylpyrrolidon ein Molekulargewicht zwischen 300 000 und 400 000 hat.

5. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die Hydroxypropylzellulose ein Molekulargewicht zwischen 250 000 und 400 000 hat.

6. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennnzeichnet, daß das Plastifizierungsmittel Propylenglykol, Glycerin, Polyethylenglykol oder Laurylalkohol ist.

7. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die organische Säure Zitronensäure oder Weinsäure ist.

8. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß das Prostaglandinanalog eine Prostaglandin F-Verbindung oder eine Prostaglandin E-Verbindung ist.

9. Vorrichtung nach Anspruch 2, dadurch gekennzeichnet, daß die heilmittelspeichernde mittlere Lage aus (a) Polyvinylpyrrolidon mit einem Molekulargewicht von 300 000—400 000, (b) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000, (c) Polyethylenglykol und (d) Zitronensäure besteht, enthaltend 16,16 - Dimethyl - *trans* - Δ^2 - PGE^1 - methylester, und die freisetzungssteuernde Lage aus (a) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000 und (b) Propylenglykol besteht.

10. Vorrichtung nach Anspruch 2, daduruch gekennzeichnet, daß die heilmittelspeichernde mittlere Lage aus (a) Polyvinylpyrrolidon mit einem Molekulargewicht von 300 000—400 000, (b) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000, (c) Laurylalkohol und (d) Weinsäure besteht, enthaltend 16,16 - Dimethyl - *trans* - Δ^2 - PGE$_1$ - methylester, und die freisetzungssteuernde Lage aus (a) Hydroxypropylzellulose mit einem Molekulargewicht von 250 000—400 000 und (b) (Glycerin besteht.

11. Verfahren zur Herstellung eines pharmazeutischen Dreilagen-Filmparäparates, dadurch gekennzeichnet, daß mit Hilfe eines Schichtstoff-Herstellungsverfahrens zusammengebaut werden; zwei filmartige Blätter einer freisetzungssteuernden Lage, die man erhält, indem eine oder mehrere Hydroxypropylzellulosen mit einem Molekulargewicht von 30 000—150 000 und ein oder mehrere Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, gewünschtenfalls eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigemischt wird, und diese entlüftet und weiters mit Hilfe eines herkömmlichen Verfahrens getrocknet wird, und ein Blatt eines Films einer heilmittelspeichernden Lage, die man erhält, indem ein oder mehrere Polyvinylpyrrolidone, Hydroxypropylzellulosen und Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigemischt wird, diese entlüftet und weiters mit Hilfe eines herkömmlichen Verfahrens getrocknet wird.

12. Verfahren zur Herstellung eines pharmazeutischen Dreilagen-Filmpräparates, dadurch gekennzeichnet, daß mit Hilfe eines Schichtstoff-Herstellungsverfahrens zusammengebaut werden: zwei filmartige Blätter einer freisetzungssteuernden Lage, die man erhält, indem ein oder mehrere Plastifizierungsmittel und Hydroxyzellulosen mit einem Molekulargewicht von 250 000—400 000 in heißem Wasser beigemischt und homogen suspendiert und dispergiert werden, gewünschtenfalls eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, zugesetzt wird, die erhaltene Suspension als eine Schicht mit einheitlicher Dicke ausgebreitet und dann ihre Temperatut auf unter 45°C gesenkt wird, um eine homogene Lösungsschicht zu erhalten, und diese dann durch Erwärmen getrocknet wird, und ein filmartiges Blatt einer heilmittelspeichernden Lage, die man erhält, indem ein oder mehrere Polyvinylpyrrolidone, Hydroxypropylzellulosen und Plastifizierungsmittel in einem organischen Lösungsmittel gelöst werden, eine Prostaglandinlösung, die eine in einem organischen Lösungsmittel gelöste organische Säure enthält, beigmeischt wird, und diese entlüftet und weiters mit Hilfe eines herkömmlichen Verfahrens getrocknet wird.

Revendications pour les Etats Contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Une préparation sous forme d'un film pharmaceutique à trois couches qui comprend une couche centrale de stockage de médicament composée d'un ou plusieurs de (a) des polyvinylpyrrolidones, (b) des hydroxypropylcelluloses, (c) des plastifiants et (d) des acides organiques, contenant un analogue des prostaglandines, et une couche de régulation de la libération de

chaque côté de ladite couche centrale, composée d'un ou plusieurs de (a) des hydroxypropylcelluloses et (b) des plastifiants, contenant ou ne contenant pas un analogue des prostaglandines.

2. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 1, dans laquelle la couche de régulation de la libération ne contient pas d'analogue des prostaglandines.

3. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 1, dans laquelle la couche de régulation de la libération contient des analogues des prostaglandines.

4. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2 ou 3, dans laquelle le poids moléculaire de la polyvinylpyrrolidone est de 300 000—400 000.

5. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2 ou 3, dans laquelle le poids moléculaire de l'hydroxypropylcellulose est de 250 000—400 000.

6. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2 ou 3, dans laquelle le plastifiant est le propylèneglycol, le glycérol, le polyéthylèneglycol ou l'alcool laurylique.

7. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2 ou 3, dans laquelle l'acide organique est l'acide citrique ou l'acide tartrique.

8. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2 ou 3, dans laquelle l'analogue des prostaglandines est un composé de type prostaglandine F ou un composé de type prostaglandine E.

9. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2, dans laquelle la couche centrale de stockage du médicament est composée de (a) une polyvinylpyrrolidone ayant un poids moléculaire de 300 000—400 000, (b) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000, (c) du polyéthylèneglycol et (d) de l'acide citrique, contenant l'ester méthylique de la 16,16 - diméthyl - *trans* - Δ^2 - PGE_1, et la couche de régulation de la libération est composée de (a) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000 et (b) du propylèneglycol.

10. Une préparation sous forme d'un film pharmaceutique à trois couches selon la revendication 2, dans laquelle la couche centrale de stockage du médicament est composé de (a) une polyvinylpyrrolidone ayant un poids moléculaire de 300 000—400 000, (b) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000, (c) de l'alcool laurylique et (d) de l'acide tartrique contenant de l'ester méthylique de la 16,16 - diméthyl - *trans* - Δ^2 - PGE_1 et la couche de régulation de la libération est composée de (a) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000 et (b) du glycérol.

11. Un procédé pour la production d'une préparation sous forme d'un film pharmaceutique à trois couches, caractérisé par l'union, selon un procédé de stratification, de deux feuilles d'un film d'une couche de régulation de la libération obtenue par dissolution d'une ou plusieurs hydroxypropylcelluloses ayant un poids moléculaire de 30 000—150 000 et d'un ou plusieurs plastifiants dans un solvant organique et, éventuellement, l'addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique et de désaération, puis un séchage selon un procédé classique, et une feuille d'un film d'une couche de stockage de médicament obtenue par dissolution d'un ou plusieurs de la polyvinylpyrrolidone, de l'hydroxypropylcellulose et des plastifiants dans un solvant organique et addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique et sa désaération puis le séchage selon un procédé classique.

12. Un procédé pour la production de préparations sous forme d'un film pharmaceutique à trois couches qui est caractérisé par l'union, selon un procédé de stratification, de deux feuilles d'un film d'une couche de régulation de la libération obtenue par addition d'un ou plusieurs des plastifiants et des hydroxypropylcelluloses ayant un poids moléculaire de 250 000—400 000 dans de l'eau chaude et mise en suspension et dispersion homogène et, éventuellement, addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique, et étalement de la suspension obtenue sous forme d'une couche d'épaisseur uniforme puis abaissement de sa température en dessous de 45°C pour obtenir une couche de solution homogène puis séchage avec chauffage, et d'une feuille d'un film d'une couche de stockage de médicament obtenue par dissolution d'une ou plusieurs des polyvinylpyrrolidones, des hydroxypropylcelluloses et des plastifiants dans un solvant organique et addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique et désaération puis séchage selon une procédé classique.

Revendications pour l'Etat Contractant: AT

1. Un dispositif pour administrer un analogue de prostaglandine qui est une structure en trois couches comprenant une couche centrale de stockage de médicament composée d'un ou plusieurs de (a) des polyvinylpyrrolidones, (b) des hydroxypropylcelluloses, (c) des plastifiants et (d) des acides organiques, contenant un analogue des prostaglandines, et une couche de régulation de la libération de chaque côté de ladite couche centrale, composée d'un ou plusieurs de (a) des hydroxypropylcelluloses et (b) des plastifiants, contenant ou ne contenant pas un analogue des prostaglandines.

2. Un dispositif selon la revendication 1, dans lequel la couche de régulation de la libération ne contient pas d'analogue des prostaglandines.

3. Un dispositif selon la revendication 1, dans lequel la couche de régulation de la libération contient des analogues des prostaglandines.

4. Un dispositif selon la revendication 2 ou 3, dans lequel le poids moléculaire de la polyvinylpyrrolidone est de 300 000—400 000.

5. Un dispositif selon la revendication 2 ou 3, dans lequel le poids moléculaire de l'hydroxypropylcellulose est de 250 000—400 000.

6. Un dispositif selon la revendication 2 ou 3, dans lequel le plastifiant est le propylèneglycol, le glycérol, le polyéthylèneglycol ou l'alcool laurylique.

7. Un dispositif selon la revendication 2 ou 3, dans lequel l'acide organique est l'acide citrique ou l'acide tartrique.

8. Un dispositif selon la revendication 2 ou 3, dans lequel l'analogue des prostaglandines est un composé de type prostaglandine F ou un composé de type prostaglandine E.

9. Un dispositif selon la revendication 2, dans lequel la couche centrale de stockage du médicament est composée de (a) une polyvinylpyrrolidone ayant un poids moléculaire de 300 000—400 000, (b) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000, (c) du polyéthylèneglycol et (d) de l'acide citrique, contenant l'ester méthylique de la 16,16 - diméthyl - *trans* - Δ^2 - PGE_1, et la couche de régulation de la libération est composée de (a) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000 et (b) propylèneglycol.

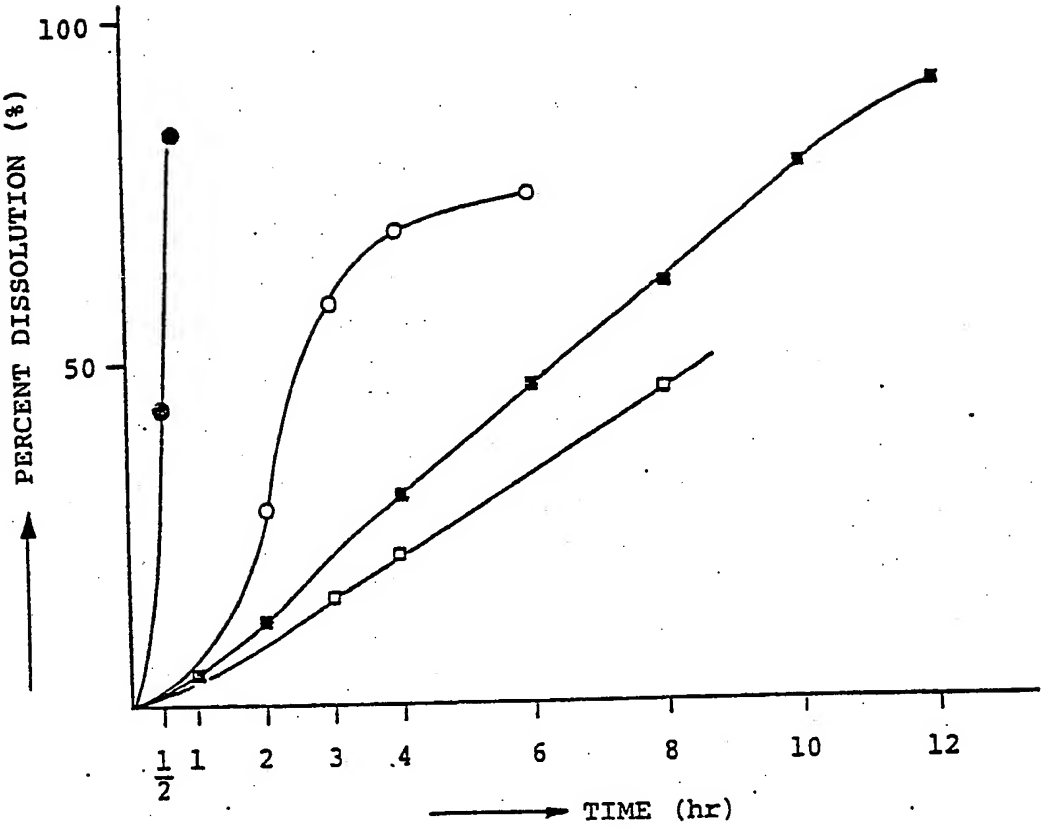
10. Un dispositif selon la revendication 2, dans lequel la couche centrale de stockage du médicament est composée de (a) une polyvinylpyrrolidone ayant un poids moléculaire de 300 000—400 000, (b) une hydroxypropylcellulose ayant un poids moléculaire de 250 000—400 000, (c) de l'alcool laurylique et (d) de l'acide tartrique contenant de l'ester méthylique de la 16,16 - diméthyl - *trans* - Δ^2 - PGE_1 et la couche de régulation de la libération est composée de (a) une hydroxpropylcellulose ayant un poids moléculaire de 250 000—400 000 et (b) du glycérol.

11. Un procédé pour la production d'une préparation sous forme d'un film pharmaceutique à trois couches caractérisé par l'union, selon un procédé de stratification, de deux feuilles d'un film d'une couche de régulation de la libération obtenue par dissolution d'une ou plusieurs hydroxypropylcelluloses ayant un poids moléculaire de 30 000—150 000 et d'un ou plusieurs plastifiants dans un solvant organique et, éventuellement, l'addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique et sa désaération, puis un séchage selon un procédé classique, et une feuille d'un film d'une couche de stockage de médicament obtenue par dissolution d'un ou plusieurs de la polyvinylpyrrolidone, de l'hydroxypropylcellulose et des plastifiants dans un solvant organique et addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique et sa désaération puis la séchage selon un procédé classique.

12. Un procédé pour la production de préparations sous forme d'un film pharmaceutique à trois couches qui est caractérisé par l'union, selon un procédé de stratification, de deux feuilles d'un film d'une couche de régulation de la libération obtenue par addition d'un ou plusieurs des plastifiants et des hydroxypropylcelluloses ayant un poids moléculaire de 250 000—400 000 dans de l'eau chaude et mise en suspension et dispersion homogène et, éventuellement, addition d'une solution de prostaglandine contenant un acide organique dissous dans un solvant organique, et également de la suspension obtenue sous forme d'une couche d'épaisseur uniforme puis abaissement de sa température en dessous de 45°C pour obtenir une couche de solution homogène puis séchage avec chauffage d'une feuille d'un film d'une couche de stockage de médicament obtenue par dissolution d'une ou plusieurs des polyvinylpyrrolidones, des hydroxypropylcelluloses et des plastifiants dans un solvant organique et addition d'une solution de prostaglandine contenant une acide organique dissous dans un solvant organique et désaération puis séchage selon un procédé classique.

Percent Dissolution (%)

in Various Preparations



: HPC film (Comparison)

: N-HP film (Comparison)

: L-HP film-(1) (Invention)

: L-HP film-(3) (Invention)